20-607

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020607

Trade Name: ARTHROTEC TABLETS

Generic Name: DICLOFENAC SODIUM/MISOPROSTOL

Sponsor: G.D. SEARLE AND COMPANY

Approval Date: 12/24/97

INDICATION(s): A FIXED COMBINATION DRUG PRODUCT FOR THE TREATMENT OF THE SIGNS AND SYMPTOMS OF OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS IN PATIENTS AT HIGH RISK FOR DEVELOPING NSAID-INDUCED GASTRIC AND DUODENAL ULCERS AND THEIR COMPLICATIONS

Review
by mail time
before release

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 020607

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Approval Letter	X			
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EA/FONSI	X			
Pharmacology Review(s)	X			
Statistical Review(s)	X			
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Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				
Administrative Document(s)	X			
Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020607

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-607

G.D. Searle & Company
Attention: Peter East
4901 Searle Parkway
Skokie, Illinois 60077

DEC 24 1997

Dear Mr. East:

Please refer to your new drug application dated December 22, 1995, received December 26, 1995, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arthrotec (diclofenac sodium/misoprostol) Tablets.

We acknowledge receipt of your submissions dated September 3, September 5, September 10, September 19, September 29, October 1, October 14, October 16, November 4, and November 20, 1997. The user fee goal date for this application is April 15, 1998.

This new drug application provides for a fixed combination drug product for the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis in patients at high risk for developing NSAID-induced gastric and duodenal ulcers and their complications.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-607. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitments specified in your submission dated

Please implement these changes as soon as possible. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Brian Strongin, Project Manager, at (301) 443-0483.

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

Paula Botstein, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020607

APPROVABLE LETTER

NDA 20-607

SEP 17 [illegible]

G.D. Searle & Company
Attention: Peter East
4901 Skokie Parkway
Skokie, Illinois 60077

Dear Mr. East:

Please refer to your new drug application dated December 22, 1995, received December 26, 1995, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Arthrotec (diclofenac sodium/misoprostol) Tablets.

We acknowledge receipt of your submissions dated February 3, March 5, March 19, May 8, June 18, July 8, August 4, and August 22, 1997. The User Fee goal date for this application is November 9, 1997.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit a satisfactory response to the following items:

Chemistry, Manufacturing, and Controls:

I. Method of Manufacture

A.

B.

Provide the which were employed in

C. Tests

The misoprostol

misoprostol. Provide for a and specification based upon your manufacturing history. You may propose a plan for reducing the number of samples tested after you demonstrate on the appropriate number of production batches that this test and specification is consistently met. In a supplement requiring Agency approval prior to implementation, please submit this plan, identifying the number of batches to be tested and your sampling plan.

II. Stability

A. Expiration Date

To date, you have submitted stability data of This is insufficient to support the proposed three (3) year expiration date. Please submit additional 25°C stability data, which you have said is complete though 2 years, along with statistical analysis.

B. Misoprostol

Your one (1) year stability data, in all proposed indicate that the the following limits (see data below):

Propose and justify revised impurity limits for individual and total based upon your two year stability data

C. Stability Protocol-Extension of Expiration Dating

You have committed to performing the for diclofenac sodium in your market stability program. Amend your stability protocol for extension of expiry to include this test.

D. Stability Protocol- Annual Market Batch Protocol

Add the for diclofenac sodium to your annual market batch stability protocol as you have committed to do.

III. Methods Validation

Submit three (3) copies of your revised methods validation package which

diclofenac sodium.

Final Printed Labeling:

In addition, it will be necessary for you to submit final printed labeling (FPL) identical in content to the enclosed marked-up draft labeling. Please submit 20 copies of the final printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1.

2.

3.

4.

5.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact Brian Strongin, Project Manager, at (301) 443-0483.

Sincerely yours,

/S/ 9-16-97

Paula Botstein, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

Enclosure: Draft Labeling

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 20-607
HFD-180/Div. Files
HFD-002/ORM
HFD-92/DDM-DIAB
HFD-180/B.Strongin
HFD-180/K.Robie-Suh
HFD-180/J.Choudary
HFD-180/G.Young
HFD-180/E.Duffy
HFD-180/G.Chen
HFD-550/J.Hyde
HFD-550/J.Witter
HFD-550/L.LoBianco
HFD-720/M.Huque
HFD-720/M.Fan
HFD-850/L.Lesko
HFD-870/M.L.Chen
HFD-870/L.Kaus
HFD-103/Office Director
HFD-105/Office Director
HFD-101/L.Carter
DISTRICT OFFICE
HFD-40/DDMAC (with draft labeling)
HFD-560/OTC (with labeling - for OTC Drug Products Only)

APPEARS THIS WAY
ON ORIGINAL

/S/ 9-16-97

Drafted by: BS/September 5, 1997/c:\wpfiles\n\20607709.0
Initialed by: EPD/September 5, 1997
KRS/September 8, 1997
PB/September 11, 1997
Final: BS/September 16, 1997

APPROVABLE (AE)

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020607

MEDICAL REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

DEC 10 '97

NDA:	20-607
Sponsor:	G. D. Searle & Co.
Drug name:	Arthrotec Tablets (diclofenac sodium/misoprostol)
Date submitted:	September 29, 1997
Date received:	September 30, 1997
Review completed:	December 4, 1997
Reviewer:	Kathy M. Robie-Suh, M.D., Ph.D.

Background:
Arthrotec Tablets, a combination product consisting of diclofenac sodium and misoprostol, was made approvable on September 9, 1997, pending revision of the proposed product labeling to be consistent with that recommended by the Agency and pending resolution of some outstanding chemistry issues. In this submission the sponsor responds to the requested labeling revisions and submits some introductory promotional material for Arthrotec.

Materials Reviewed:
This submission consists of two volumes (Vols. 13.1 and 13.2) containing revised labeling, with sponsor's justification, proposed journal advertisement and copies of supporting references.

Reviewer's Comments:

I. *Revised Labeling: General:*

The labeling submitted by the sponsor is acceptable with exception of the changes I have indicated in the draft labeling attached to this review as Appendix A. [Note: Only pages on which I recommend a change from the labeling submitted by the sponsor are included].

In addition, I have the following specific comments regarding the sponsor's revised labeling:

- The sponsor's proposal to change the wording of the indication to "...requires nonsteroidal anti-inflammatory drug (NSAID) therapy and has one or more specific risk factors for..." is not acceptable. Identification of the target patient population as "high risk" should be retained. Data was not collected or analyzed to evaluate the response and/or safety of Arthrotec in patients identified with respect to particular risk factors. The weighting of the risk factors that contribute to the benefit/risk assessment for the use of

this drug in an individual patient is part of the practice of medicine and should not be incorporated in the labeling unless specific data is provided.

- The **SPECIAL DOSING CONSIDERATIONS** section should remain. It provides to the physician clear information about the efficacy and limiting side effects of the misoprostol component of Arthrotec as related to misoprostol dose.

- The formatting of the **PRECAUTIONS** section is confusing. The sponsor should make clear by use of bolding, italics, and or indentation the levels of subsections.

- The sponsor should provide a table identifying by clinical trial the 481 patients with history of GI ulcers.

- Regarding the revisions made to the CLINICAL PHARMACOLOGY section, I defer to FDA Biopharmaceutic recommendations.

- Regarding the deletion of the sentence "In a 21-month mouse carcinogenicity study, ---", I defer to the recommendation of FDA Pharmacology.

- The paragraph the sponsor proposes to add to the Patient Information leaflet (submitted to the Agency, 11/20, 97) is acceptable.

II. *Revised Labeling: Adverse Events:*

In response to the Agency's request that the Adverse Events section be simplified, the sponsor has eliminated a number of previously listed adverse events from the labeling. Events eliminated included events the sponsor considered: (1) unrelated to treatment and/or clinically unimportant, (2) unrelated to treatment, (3) described with vague terms of uncertain clinical relevance.

In reviewing these deletions I have considered, in addition to the sponsor's rationale, whether the event was reported in the Arthrotec adverse event database at a frequency of 1% or greater, whether there have been 2 or more reports of the event in the FDA spontaneous reporting adverse events database for patients taking both misoprostol and diclofenac sodium, whether the events currently are listed in the recommended misoprostol labeling and whether the events currently are listed in the NSAID class labeling.

I would recommend retaining the following:

Body as a Whole: asthenia (has 8 reports in AE database)

Female Reproductive Disorders: Menstrual disorder (term is vague admittedly but may be clinically meaningful for menstrual irregularities patients may have difficulty articulating).

In addition, I would recommend retaining in the Adverse events section mention of most of those events described elsewhere in the labeling (e.g., Precautions section). These events include:

Cardiovascular System: CPK increased, LDH increased.

GI: Gastric ulcer, duodenal ulcer, ulcerative stomatitis

Liver and Biliary System: Abnormal hepatic function, bilirubinemia

Metabolic and Nutritional: Periorbital edema, glycosuria.

Platelet, Bleeding and Clotting Disorders: Bruising

Urinary System: Papillary necrosis.

III. *Proposed Promotional Material:*
The material does not clearly convey that Arthrotec is a combination product consisting of two active drugs. The sponsor repeatedly refers to Arthrotec as being an NSAID. Arthrotec is an NSAID-containing combination drug product. The sponsor should not obscure the fact that diclofenac sodium is the NSAID in this product and the mucosal protective effect comes not from the NSAID but from the misoprostol component.

APPEARS THIS WAY
ON ORIGINAL

/S/

Kathy M. Robie-Suh, M.D., Ph.D. 12/4/97

cc:
NDA 20-607
HFD-180
HFD-180/LTalarico /S/ 12-10-97
HFD-180/KRobie-Suh
HFD-180/BStrongin
HFD-180/JChoudary
HFD-180/EDuffy
HFD-550
f/t 12/4/97 jgw
MED\N\20607712.0KR

APPEARS THIS WAY
ON ORIGINAL

APPENDIX A

26 Page(s) Redacted

DRAFT LABELING

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA:	20-607
Document Identification:	AZ; SEP 10 [illegible] BL
Sponsor:	G. D. Searle & Co.
Drug name:	Arthrotec (diclofenac sodium/misoprostol) Tablets
Date submitted:	May 8, 1997; June 18, 1997
Date received:	May 9, 1997; June 19, 1997
Review completed:	August 27, 1997
Reviewer:	Kathy M. Robie-Suh, M.D., Ph.D.

Background:
Arthrotec is a fixed dose combination of diclofenac sodium and misoprostol intended for use in treating the signs and symptoms of osteoarthritis and rheumatoid arthritis in patients at high risk of developing NSAID-induced gastrointestinal ulcers and their complications. Marketing of two strengths of the drug is proposed: Arthrotec 50 (diclofenac 50mg/misoprostol 200mcg) and Arthrotec 75 (diclofenac 75mg/misoprostol 200mcg). The diclofenac component is to provide antiarthritic efficacy and the misoprostol component is to provide antiulcer protection of the gastrointestinal mucosa.

On March 26, 1997 the sponsor was sent a non-approval letter stating as reasons for non-approval, (1) unresolved clinical and statistical issues (particularly with regard to safety and efficacy of the diclofenac component in rheumatoid arthritis) and (2) unresolved bioequivalence issues (particularly with regard to failure of the sponsor to demonstrate bioequivalence between marketed Cytotec and the Arthrotec formulations to be marketed, even though Cytotec studies were cited in support of prevention of gastrointestinal ulcers by misoprostol). A copy of the Agency's March 26, 1997 letter is attached to this review as Appendix A.

In the May 8, 1997 submission the sponsor responded to the Office of Drug Evaluation III's action letter of March 26, 1997. In addition, the sponsor met with the Agency on June 4, 1997 to discuss its response to the action letter. At that meeting the sponsor presented preliminary results from new bioequivalence studies (Study 359 and Study 360) and indicated that analysis of these studies should resolve the outstanding bioequivalence issues. Full reports of these two bioequivalence studies were to be submitted to FDA for

review by Biopharmaceutics. [Minutes from that meeting have not yet been finalized]. In the June 18, 1997 submission the sponsor has provided revised proposed labeling for Arthrotec.

Materials Reviewed:
The May 8, 1997 submission consists of a single volume containing a cover letter in two sections: "Section I - NDA Background and Rationale" and "Section II - Responses to Specific Issues Identified in the Action Letter", and supporting material for these responses. The only new information included relates to the randomization procedure for Study 349 [item I.A. in the cover letter and Attachment 1 of the 5/8/97 submission].

The June 18, 1997 submission consists of revised annotated proposed labeling for Arthrotec.

I have reviewed the material submitted and my comments follow below. For the most part I have confined my comments to the activity of the misoprostol component of Arthrotec.

Reviewer's Comments:
It should be understood that the major clinical issue in this application for misoprostol, does not have to do with efficacy of the drug *per se*. Both diclofenac sodium and misoprostol are already approved or recommended for approval for the indications for which they are to be used in the proposed combination product. Rather the issue here is one of dose. While optimization of drug dose for efficacy is not required for approval of drug products, in this case the "efficacy" of misoprostol has to do with reducing a treatment risk to patients rather than treating some disorder; therefore, in this case dose should be optimized, to the extent reasonably possible, to provide maximum <u>safety</u> for the targeted high-risk patients.

At this time FDA Biopharmaceutics review of bioequivalence Studies 359 and 360 is pending. [It is my understanding that though some data from these studies has been sent by the sponsor, full reports of these studies have not yet been submitted]. Summarized in the following tables and paragraphs are my understanding and assessment of the bioequivalence and clinical issues based on the FDA reviews completed as of 8/28/97. [Note: Also, please refer to my review of the Arthrotec NDA 20-607 submission dated December 5, 1996, pages 8 through 10].

<u>Bioequivalence</u>: For the diclofenac component, FDA Biopharmaceutics has concluded the following with regard to bioequivalence to Voltaren:

Accepting these conclusions, the following clinical inferences can be made with regard to the Arthrotec clinical study formulations, marketed Cytotec and Voltaren, and the Arthrotec formulations intended for marketing.

1. For Arthrotec 50,
   was found to be bioequivalent to marketed Cytotec + Voltaren with regard to both diclofenac and misoprostol. Therefore, the efficacy results (for both arthritis treatment and ulcer prevention) of Clinical Trials 349 and 352 may be applied to the already marketed Cytotec and Voltaren.

2. There is no direct or indirect link based on clinical studies between Arthrotec 50 and the Arthrotec 50 formulation proposed for marketing (US Product B).

   The sponsor proposes bridging the gap by <u>assuming</u> equivalency between Arthrotec 50 and which differ only with regard to manufacturing site and duplex versus simplex process in manufacture of misoprostol drug substance. These changes should not affect the bioavailability of the drug (personal communication, GChen, FDA Chemistry). [Note: The assumption of equivalency between Arthrotec 50 and appears to have tacitly been accepted by the Agency, based on the statements regarding Arthrotec 50 at the top of page 4 of the non-approval letter]. This allows a conclusion of bioequivalence of Arthrotec 50 proposed US Product B to Voltaren (for diclofenac) but not to Cytotec (for misoprostol). The proposed would supply as little as 75.2% of the misoprostol acid Cmax provided by Canadian Arthrotec; however, the misoprostol acid AUC provided is the same for the two.

3. For Arthrotec 75, (which was used in pivotal clinical trials 349 and 352) was <u>not</u> found to be bioequivalent to marketed Cytotec + Voltaren. Based on the single dose, fasting bioequivalence Study 346, Clinical Supply III supplies as much as 125.9% of diclofenac AUC and as little as 60.5% of diclofenac Cmax provided by Voltaren and as much as 125.4% of misoprostol acid AUC and as much as 134.6% of misoprostol acid Cmax provided by Cytotec. Thus, patients in Studies 349 and 352 possibly received a higher dose of misoprostol than would have been supplied by marketed Cytotec.

   However, in the multiple dose, fasting bioequivalence Study 347, Arthrotec 75 was found to be bioequivalent to Voltaren for AUC but not for Cmax. (Cytotec bioequivalence was not examined in this study).

4. Arthrotec 75 proposed has been demonstrated to be equivalent to the formulation used in the pivotal clinical trials (Studies 349 and 352). Therefore, the efficacy results from these studies may be used to support the approval of the Arthrotec 75 formulation proposed for marketing.

Thus, Arthrotec 50 proposed for marketing appears to be bioequivalent to marketed Voltaren but not to Cytotec (low Cmax). Arthrotec 75 proposed for marketing appears not

to be bioequivalent to marketed Cytotec + Voltaren for either diclofenac or misoprostol. It should be borne in mind that these conclusions are based on interpretation of as series of variously "linked" studies done at different times, which may not be as reliable as a clean head-to-head comparison of the bioavailability of the products the sponsor proposes to market versus the already marketed individual components (Cytotec and Voltaren). Therefore, as in my review of 12/5/96, I recommend that the sponsor perform a direct comparison bioequivalence study of Arthrotec 50 versus Cytotec + Voltaren and of Arthrotec 75 versus Cytotec + Voltaren.

Clinical Studies: [Note: Also, please refer to my Medical Officer's Reviews of Arthrotec NDA 20-607, dated 12/5/96, pages 102 through 111 and dated 3/7/97].

The Arthrotec NDA submission contained 6 clinical studies in which the ulcer frequencies in patients treated with diclofenac/misoprostol combination were compared to the rates in patients treated with NSAID alone. Five of these trials studied Arthrotec 50 (Studies 349, 296, 321, 289, and 269) and two studied Arthrotec 75 (Studies 349 and 013).

For Arthrotec 50: In three of these trials (Studies 296, 289, and 269) Arthrotec dosing was not randomized but rather Arthrotec 50 was given BID or TID at the discretion of the investigator and dosing regimen could be changed during the study. Furthermore, in one study (Study 289) there was a significant difference between treatments (Arthrotec versus diclofenac alone) in rate of endoscopy among patients who were discontinued due to adverse events favoring Arthrotec.

In Study 321 Arthrotec 50 TID was compared to piroxicam and naproxen alone and was found to be superior to each NSAID in this study for both prevention of gastric ulcer and duodenal ulcer. There was no diclofenac alone arm; therefore, this study is not useful in establishing the protective effect of misoprostol in the Arthrotec (combination product) tablet.

In Study 349 in osteoarthritis patients Arthrotec 50 TID was compared to diclofenac 50mg TID, Arthrotec 75 BID and placebo. Treatment regimens were randomized and not changed during the study. Arthrotec 50 TID and Arthrotec 75 BID each was found to be superior to diclofenac 50mg TID alone in preventing gastric ulcer ($p = 0.016$ and 0.046, respectively), but not for preventing duodenal ulcer ($p = 0.756$ and 0.092, respectively). A question was raised regarding the randomization for Study 349. The sponsor has provided information indicating that "Study 349 was randomized using a single randomization plan and a block size of 11 (a pre-specified distribution of 3, 3, 3 and 2 for patients in the three active and placebo groups, respectively)" and that though drug supplies were sent out in blocks of 11, "32 of the 55 investigators (58%) enrolled 10 or fewer patients...thereby leaving over half of the blocks incomplete" and this by chance led to the final imbalance in patient numbers among the treatment arms. This explanation is adequate and consistent with my previously expressed assessment of the situation. (See my E-Mail to WChambers dated 3/18/97 which is attached to this review as Appendix B). Importantly, the treatment groups were well-balanced with regard to demographics and baseline characteristics.

In conclusion, with regard to misoprostol activity, for Arthrotec 50 TID there is one adequate and well-controlled clinical trial (Study 349) demonstrating prevention of gastric ulcer while no adequate and well-controlled studies demonstrate prevention of duodenal ulcer.

For Arthrotec 75: Arthrotec 75 was studied in two trials, Study 349 and Study 013. In Study 349, which was an adequate and well-controlled clinical trial, Arthrotec 75 BID was found to be superior to diclofenac 50mg BID alone in preventing gastric ulcers ($p = 0.046$) but not for preventing duodenal ulcers ($p = 0.092$).

Study 013 was not an adequate and well-controlled clinical trial. Major deficiencies included lack of baseline endoscopy, inadequate measures taken to protect the blind, and lack of bioequivalence information to link the sustained release diclofenac sodium formulation used as the comparator in this study to any diclofenac sodium product approved in the U.S.

In conclusion, with regard to misoprostol activity, for Arthrotec 75 BID there is one adequate and well-controlled clinical trial (Study 349) demonstrating prevention of gastric ulcers while no adequate and well-controlled studies demonstrate prevention of duodenal ulcers.

Bioequivalence + Clinical Studies:
Arthrotec 50: Arthrotec 50 pivotal clinical trial formulation and the formulation proposed for marketing are "almost" bioequivalent to marketed Cytotec + Voltaren with the only deficiency being that the Cmax for the proposed Arthrotec 50 product being about 75.2% that of marketed Cytotec. Considering this, the data from the Arthrotec database may be applied to marketed Cytotec (giving one additional trial, Study 349 supporting efficacy of misoprostol 200mcg BID in preventing gastric ulcers).

Accepting Cytotec efficacy data as demonstration of efficacy of misoprostol effectiveness in Arthrotec 50 given TID necessitates an acceptance that the Cmax for misoprostol is not clinically important in the dosing of this drug. We don't know this to be the case, although for drug therapies requiring repeated dosing, steady state blood levels and AUC are usually more important. The sponsor's claim that the difference in misoprostol acid Cmax with Arthrotec 50 is due to variability between and within patients rather than to a real difference from the Cytotec may be resolved by a direct bioavailability comparison of the two products. There is no compelling public health incentive to relax Agency standards to obtain approval of this drug. Both component drugs misoprostol (Cytotec) and diclofenac sodium (Voltaren) are already available to the public.

Also, in considering application of the Cytotec database to Arthrotec, it should be borne in mind that no diclofenac sodium treated patients are in the Cytotec database as currently reflected in the Cytotec labeling. (Voltaren Tablets was approved July 28, 1988; Cytotec was approved December 27, 1988). Most of the patients in the Cytotec database were on ibuprofen, naproxen, or piroxicam.

Arthrotec 75: The data submitted indicate that Arthrotec 75 is not bioequivalent to Cytotec + Voltaren for either diclofenac (misses on both AUC and Cmax) and misoprostol acid (misses on both AUC and Cmax). Cytotec data should not be applied to Arthrotec 75 and Arthrotec 75 data should not be applied to Cytotec.

There is one clinical trial (Study 349) demonstrating efficacy of Arthrotec 75 BID in preventing gastric ulcers.

Labeling Review:
A review of the proposed labeling for Arthrotec at this time makes sense only if it is assumed that the outstanding bioequivalence issues will be satisfactorily resolved. (Otherwise the drug would not be approvable). Therefore, the labeling review which follows makes this assumption.

General Discussion: **Assuming satisfactory resolution of outstanding bioequivalence issues**, Cytotec clinical data could be applied to Arthrotec and Arthrotec clinical data could be applied to Cytotec. Efficacy of Arthrotec and Cytotec will have been adequately established as follows:

Studies in Which Efficacy Has Been Demonstrated for Various Misoprostol Regimens

Drug Product	Misoprostol Dosing Regimen		Gastric Ulcer	Duodenal Ulcer
Cytotec	200mcg	QID	Study 053 Study 002 Study 003 Study 041	Study 053 Study 041
		TID	Study 053[a] Study 320 Study 349	Study 053
		BID	Study 053 Study 349	Study 053
	100mcg QID		Study 002[b]	---
Arthrotec 50	200mcg	QID	Study 053 Study 002 Study 003 Study 041	Study 053 Study 041
		TID	Study 053[a] Study 320 Study 349	Study 053
		BID	Study 053 Study 349	Study 053
Arthrotec 75	200mcg	[redacted]	[redacted]	[redacted]
		TID	Study 053[a] Study 320 Study 349	Study 053
		BID	Study 053 Study 349	Study 053

[redacted] diclofenac dose would exceed that recommended for osteoarthritis but not that recommended for rheumatoid arthritis

[redacted] diclofenac dose would exceed that recommended for osteoarthritis but possibly would be allowed for rheumatoid arthritis

[redacted] diclofenac dose would exceed that recommended for osteoarthritis and rheumatoid arthritis

[a] misoprostol 200mcg TID therapeutically equivalent to misoprostol 200mcg QID.
[b] misoprostol 200mcg QID was superior to 100mcg QID
reviewer's original table

Bioequivalence of Arthrotec 50 and Arthrotec 75 to Marketed Voltaren

	Demonstrated to be Bioequivalent to Voltaren? (Yes/No)		Comments
	AUC	Cmax	
Arthrotec 50	Yes	Yes	Indirect: + Cytotec
	Not determined.	Not determined.	No direct comparison. This product was compared only to Arthrotec 50* to which it was found to be bioequivalent with regard to diclofenac AUC and Cmax.
Arthrotec 75	No.	No.	
	No.	No.	Indirect:

For the misoprostol component, FDA Biopharmaceutics has concluded the following with regard to bioequivalence to Cytotec:

Bioequivalence of Arthrotec 50 and Arthrotec 75 to Marketed Cytotec

	Bioequivalent to Cytotec? (Yes/No)		Comments
	AUC	Cmax	
Arthrotec 50	Yes	Yes	
	Not determined.	Not determined.	No direct comparison. This product was Arthrotec 50* to which it was found to be bioequivalent with regard to misoprostol AUC but <u>not</u> Cmax.
Arthrotec 75	No.	No.	
	No.	No.	

Using this information Arthrotec 50 QID could be approved and labeled for prevention of gastric and duodenal ulcers in rheumatoid arthritis patients at high risk of developing NSAID-induced gastrointestinal ulcers and their complications. Arthrotec 50 TID could be approved for prevention of gastric ulcers in osteoarthritis and rheumatoid arthritis patients at high risk for development of NSAID-induced gastrointestinal ulcers and their complications but who are unable to tolerate misoprostol 200mcg QID for prevention of gastric and duodenal ulcers. Arthrotec 50 BID could be approved for prevention of gastric ulcers in osteoarthritis and rheumatoid arthritis patients at high risk for development of NSAID-induced gastrointestinal ulcers and their complications but who are unable to tolerate either misoprostol 200mcg QID for prevention of gastric and duodenal ulcers or misoprostol 200mcg TID for prevention of gastric ulcers (and which may be superior to misoprostol 200mcg BID for prevention of gastric ulcers).

Arthrotec 75 given BID could be approved for prevention of gastric ulcers in osteoarthritis and rheumatoid arthritis patients at high risk for development of NSAID-induced gastrointestinal ulcers and their complications but who are unable to tolerate either misoprostol 200mcg QID for prevention of gastric and duodenal ulcers or misoprostol 200mcg TID for prevention of gastric ulcers (and which may be superior to misoprostol 200mcg BID for prevention of gastric ulcers).

Arthrotec 75 given TID might be allowed for prevention of gastric ulcers in high risk rheumatoid arthritis patients unable to tolerate misoprostol 200mcg QID. However, this regimen would provide 225 mg of diclofenac daily, which though not clearly in the dose range recommended for rheumatoid arthritis, could be interpreted as the highest recommended dose, based on the current diclofenac sodium labeling. Arthrotec 75 QID clearly would exceed the allowable daily dose of diclofenac for any arthritis patients..

Draft Labeling: A copy of the sponsor's proposed labeling with my proposed revisions written in is attached to this review as Appendix B.

I also have the following general comments regarding the labeling:

1. The wording of the indication should be changed from "increased risk..." to "high risk..." The term 'increased risk...' does not adequately identify the target population. (Presumably, by taking an NSAID everyone increases his or her risk of developing gastrointestinal ulcers). The wording "...at high risk of developing a gastric or duodenal ulcer or of developing complications from gastric or duodenal ulcers associated with the use of the NSAID" is more descriptive of the target population and is consistent with the current labeling for Cytotec.

2. There should be consistency between the Arthrotec labeling and the Cytotec labeling in the information and wording provided with regard to misoprostol.

3. I have not commented on the "Pharmacokinetics of ARTHROTEC" section. This should be reviewed by Biopharmaceutics.

4. I have not commented on the "Analgesic Properties of ARTHROTEC" section or on the "CLINICAL STUDIES: Osteoarthritis" or "CLINICAL STUDIES: Rheumatoid Arthritis" sections. These should be addressed by the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products (HFD-550).

5. Though I have reviewed the "Gastrointestinal (GI) Effects - Risks of GI Ulceration, Bleeding and Perforation" section under WARNINGS, HFD-550 should review this section as well.

APPEARS THIS WAY
ON ORIGINAL

/S/

Kathy M. Robie-Suh, M.D., Ph.D. 8/29/97

cc:
NDA 20-607
NDA 19-268
HFD-180
HFD-180/LTalarico
HFD-180/KRobie-Suh
HFD-181/BStrongin
HFD-180/JChoudary
HFD-180/EDuffy
HFD-710/MFan
HFD-550/JWitter
f/t 8/29/97 jgw
MED\N\20607708.1KR

/S/ 9-10-97

APPEARS THIS WAY
ON ORIGINAL

APPENDIX A

7 Page(s) Redacted

Duplicate

Not Approvable LETTER

APPENDIX B

101 Page(s) Redacted

DRAFT

LABELING

Medical Officer's Review of Request for Consultation (HFD-180)

SEP - 2 1997

NDA 20-607	**Submitted date (HFD-550):**	July 10, 1997 August 5, 1997
	Submitted date (reviewer):	July 11, 1997
	Review completed:	August 27, 1997

Sponsor: G.D. Searle
4901 Searle Parkway
Skokie, Ill. 60077

Drug: Arthrotec (diclofenac/misoprostol)

Submitted: Proposed U.S. Labeling for Arthrotec (along with current labeling for Cytotec and Diclofenac)

The comments that follow are based, to some extent, on how this reviewer thinks clinical colleagues will receive this label (in the context of busy clinical schedules) and with the understanding that this reviewer has only reviewed Protocol I88-94-02-013 and not the other protocols submitted to HFD-550; protocol 013 is not being used to support the Arthrotec label according to the annotations in the label.

1. As a slight digression, the Cytotec label is confusing in the **Pharmacodynamics** section with the sentence beginning "Misoprostol can increase bicarbonate and mucous production..." It is unclear how this sentence serves as logic for the following sentence.

2. Could readers be referenced to the individual Cytotec and Diclofenac labels and portions of the Arthrotec label be removed? There has obviously been editing of the information from the individual labels that has helped form the Arthrotec label. However, some of the edited information may be useful to some readers. For example, in the **Clinical Pharmacology** section of the Cytotec label, there is a table that may help to understand the statement that studies have not found that food or antacid effect the clinical results of misoprostol. To the average reader, the differences in Cmaxs between fasting and food are canceled by the AUC information. On the other hand, in the Arthrotec label (page 5). Table 1 seems to be confusing since it is for single doses in a fasted condition but just above is the statement that food and antacid can effect total availability of misoprostol. Table 1 itself is confusing because one must assume that under the "Treatment" section, the Cytotec and Voltaren doses are comparable to those used in the Arthrotec formulations; but this is not stated directly in the table.

3. The **Analgesic Properties of Arthrotec** section is confusing in the second line of the second paragraph. Does the "50 mg diclofenac sodium coadministered with 200 mcg of misoprostol" mean these were given as separate components or was it Arthrotec 50? The sentence also may read more clearly with "or placebo" vs. "and placebo". It may also be useful to have N's for the various treatment groups from the total of 292.

4. In the **Clinical Studies** section under **Osteoarthritis,** it should be noted in the first paragraph that 200 mg/day of diclofenac is **NOT** recommended in the diclofenac (Voltaren-XR) labeling. In the final paragraph, it is unclear if the piroxicam in QD or BID (like naproxen); the usual dose of piroxicam is 20 mg /day. Is this the same study in Table 3 (page 10) where piroxicam was BID?

5. In the **Upper Gastrointestinal Safety** section, how are ulcers defined in all these studies? Are they all by endoscopic analysis, clinical presentation, both? This should be clarified in the labeling.

6. In the **Indications and Usage** section, will the reference to the Singh paper go with the label since other authors do not necessarily agree with Dr. Singh (i.e. many believe gender may have a role)? Do you think "older age" needs to be defined to some extent i.e. elderly may be more appropriate (i.e. see the Geriatric Use section of the label on page 22 which calls into question the concept of increased risk with "age". Similarly, the Long Term Administration-page 24 of label-would appear to contradict the statement in the Warnings section-GI effects- that states that "These trends continue thus..." in the first paragraph, page 12). In fact, the population of women who are candidates for Arthrotec should probably NOT include those women who are of child-bearing potential. Should the list of risk factors be eliminated since it is already in the GI effects section? At the very least, should the risk factor list read something like "Factors that may increase risk include..."

7. In the **GI effects** section on page 12, the second word of the second paragraph is misspelled (i.e. shoud).

8. Under **Drug Interactions** on page 20 (Other Drugs), doxycycline is misspelled in the second line.

9. Under **Animal Toxicology** on page 20, toxicology is misspelled on the second line.

10. Under **Adverse Reactions/Gastrointestinal** it is of interest that "fewer than 8% of patients" receiving Arthrotec discontinued therapy for diarrhea and abdominal pain while in the Cytotec label this was "about 3.5% of patients".

11. In the **Metabolic and Nutritional** section on page 25, what is NPN?

12. On page 26, I believe the correct spelling for *italicised* is italicized.

13. The **Special Considerations: Arthrotec** on page 29 helps to clarify some of the difficult therapeutic issues associated with these fixed combination products.

APPEARS THIS WAY
ON ORIGINAL

/S/

(James Witter, M.D., Ph.D. Medical Officer)

cc HFD-550
HFD-180
HFD-550/MO/Witter

See also separate Deputy Director review 9-2-97

/S/

APPEARS THIS WAY
ON ORIGINAL

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
AMENDMENT TO MEDICAL OFFICER'S REVIEW

NDA: 20-607

APR - 7 1997

Document Identification: N

Sponsor: G. D. Searle & Co.

Drug name: Arthrotec Tablets (diclofenac sodium/misoprostol)

Date submitted: December 22, 1995

Reviewer: Kathy M. Robie-Suh, M.D., Ph.D.

Following are some corrections to some errors which I have noted in my original review of this submission dated December 5, 1996.

1. On page 9 under *"Arthrotec 75"* the first sentence should read as follows:

> "For Arthrotec 75, the drug used in the pivotal clinical trials was compared with regard to both diclofenac and misoprostol to the product the sponsor intends to market and the two formulations were found to be bioequivalent."

2. On page 29 in the table under the section "Duodenal Ulcer + Pyloric Channel Ulcer" the numbers should be as follows:

Duodenal Ulcer + Pyloric Channel Ulcer:		
Comparison	Numbers of Patients	2-sided p-value
DU + PU: D75 vs. Placebo	9/154 vs. 1/91	0.096
DU + PU: D50/M200 vs. D75	8/152 vs. 9/154	0.756
DU + PU: D75/M200 vs. D75	4/175 vs. 9/154	0.092
DU + PU: D75/M200 vs. D50/M200	4/175 vs. 8.152	0.238

3. On page 47, line 5, the number "0.060" should be changed to "0.092".

4. On page 47, line 6, the number "7.1%" should be changed to "5.3%".

5. On page 67, the first sentence of the first paragraph of text should read as follows:

> "Significantly fewer diclofenac/misoprostol patients had duodenal (including pyloric channel) ulcers as compared to piroxicam patients ($p = 0.002$) but not as compared to naproxen patients ($p = 0.081$)."

6. In the Summary Table on page 103, for Study IN2-89-02-289, patients randomized should be "342 RA patients" and for Study EB2-87-02-269 patients randomized should be "384 OA or RA patients".

7. In the Summary Table on page 107, for Study 349 under the "Placebo" column the second entry should be "9/154" instead of 11/154. Under the Arthro I vs. NSAID alone column the second entry should be "0.756" instead of 0.637 and under the Arthro II vs. Diclo column the second entry should be "0.092" instead of 0.060.

8. On page 110, the first sentence of the last paragraph should read as follows:

> "For Arthrotec 75, the formulation proposed for marketing was demonstrated to be bioequivalent to the clinical trial formulation) which was <u>not</u> shown to be bioequivalent to Cytotec + Voltaren with regard to misoprostol or diclofenac."

APPEARS THIS WAY
ON ORIGINAL

/S/
Kathy M. Robie-Suh, M.D., Ph.D. 4/7/97

cc:
NDA 20-607
HFD-180
HFD-180/SFredd
HFD-180/KRobie-Suh
HFD-181/BStrongin
HFD-180/JChoudary
HFD-180/EDuffy
HFD-710/MFan
HFD-550
HFD-870/H-RChoi
f/t 4/3/97 jgw
MED\N\20607704.0KR

APPEARS THIS WAY
ON ORIGINAL

MEDICAL OFFICER CONSULT REVIEW

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products

NDA #: 20-607

NAME: Arthrotec (diclofenac sodium/misoprostol)

SPONSOR: G. D. Searle & Co.
4901 Searle Parkway
Skokie, Illinois 60077

TYPE OF SUBMISSION: Commercial Pharmaceutical

DATE OF SUBMISSION: December 22, 1995 **CDER:** December 26, 1995

DATE OF REVIEW: November 6, 1996; amended December 2, 1996

REVIEWER: Rosemarie Neuner, MD, MPH

CSO: Ms. Lissante LoBianco

Diclofenac is a benzene acetic acid derivative that belongs to the nonsteroidal anti-inflammatory class of drugs (NSAIDs). It has been approved for marketing in the United States (U.S.) since 1988 for the acute and chronic symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The recommended dose range for diclofenac sodium in the treatment of rheumatoid arthritis is 150 to 200 mg per day in divided doses; for osteoarthritis the recommended dose range is 100 to 150 mg per day in divided doses. Misoprostol is a synthetic prostaglandin E_1 analogue that is approved for marketing in this country for the prevention of NSAID-induced gastric ulcers in patients at high risk for developing gastric ulcers or to the complications associated with gastric ulceration. The recommended dose for misoprostol (Cytotec) is 200 mcg qid, but 100 mcg can be used if the higher dose is not tolerated. The Sponsor of this application, G. D. Searle & Co., is now requesting approval for Arthrotec I and II Tablets which are fixed dose combinations of diclofenac sodium and misoprostol. Arthrotec I contains 50 mg of diclofenac sodium and 200 mcg of misoprostol while Arthrotec II is comprised of 75 mg of diclofenac sodium and 200 mcg of misoprostol. The Sponsor's rationale for this fixed dose combination is for potentially better patient compliance and convenience by those arthritis patients who are at greatest risk for NSAID-induced gastric ulceration. In 1993 an earlier application from this Sponsor had been found to be unacceptable for NDA filing due to a number of problems which included lack of placebo-controlled trials, short duration of treatment and limited dosing options due to just one fixed combination dose form (Arthrotec I - diclofenac 50 mg/misoprostol 200 mcg).

In support of the proposed treatment indications of rheumatoid arthritis and osteoarthritis, the Sponsor has submitted the results of 9 clinical trials for review, 2 of these trials were done in the United States in response to the deficiencies noted by the FDA in 1993. A total of 1,011 patients were exposed to the Arthrotec combinations in these 9 clinical trials. Four of these trials were conducted in osteoarthritis patients while 3 trials were done in rheumatoid arthritis patients. Of the remaining 2 trials, 1 is a pharmacokinetics trial done in rheumatoid arthritis patients. The last trial is a study using a mixed population of rheumatoid arthritis and osteoarthritis patients. Since this

NDA was filed in the Division of Gastrointestinal and Anticoagulation Drug Products, HFD-180, this review is an efficacy consult limited to a discussion of this fixed combination product's efficacy in the treatment of osteoarthritis and rheumatoid arthritis. The 4 osteoarthritis trials will be discussed first, followed by the rheumatoid arthritis trials. The results of the mixed population trial and the pharmacokinetic trial will be briefly discussed last. A full discussion of drug safety including endoscopy results can be found in the medical officer's NDA review from HFD-180.

Section I - Osteoarthritis Trials

A COMPARATIVE STUDY OF THE EFFICACY AND UPPER GASTROINTESTINAL SAFETY OF DICLOFENAC 75 MG BID, DICLOFENAC 50 MG/MISOPROSTOL 200 MCG TID, AND DICLOFENAC 75 MG/MISOPROSTOL 200 MCG BID IN TREATING THE SIGNS AND SYMPTOMS OF OSTEOARTHRITIS (OA).

Protocol NN2-94-02-349

Design:

This was a multi-center, double-blind, placebo-controlled trial with 4 parallel treatment arms in which patients with American College of Rheumatology (ACR) functional class I-III OA of the knee and/or hip, and previously documented histories of peptic ulcer disease were randomized to receive either diclofenac 75 mg b.i.d., Arthrotec I (diclofenac 50 mg/misoprostol 200 mcg) t.i.d., Arthrotec II (diclofenac 75 mg/misoprostol 200 mcg) b.i.d., or placebo for 6 weeks. Prior to being randomized to one of the 4 comparative treatment groups, patients had to demonstrate a clinical flare of their OA, as well as undergo a 3 to 14 -day washout period of all ongoing therapy with nonsteroidal antiinflammatory drugs (NSAIDs) or analgesics. Once randomized, patients were permitted to ingest up to 6 Amphogel tablets a day for the symptomatic relief of GI discomfort while participating in the study. No other treatment with anti-ulcer medications were permitted for the duration of the trial. Rescue acetaminophen was permitted for the short-term treatment of headaches and other mild ailments, but could not be used within 24-hours of an efficacy evaluation.

Efficacy and safety evaluations were performed at the baseline visit, and at Weeks 2 and 6 of the study. All patients were evaluated for the following three primary efficacy parameters for OA: the Physician's Global and the Patient's Global assessments of arthritis condition via categorical scales; and the OA Severity Index. The OA severity index was a composite score, based on a maximum score of 24, comprised of patient self-assessments related to the following: severity of OA pain, walking distance and activities of daily living. Secondary efficacy variables were also performed and included: a Patient's Assessment of Arthritis Pain via a 10 cm visual analogue scale (VAS), a Functional Capacity Classification, and Incidence of Patient

Withdrawal Due to Lack of OA Efficacy. A quality of life evaluation, the SF-36 Health Survey, was added as a protocol amendment 3 months after the trial was started. Since the SF-36 Health Survey was started after the study was underway, only patients that were entered into the trial after it had been introduced were evaluated by this method. Safety was assessed by upper gastrointestinal (GI) endoscopy, routine lab analyses, physical exams and adverse event monitoring. Upper GI endoscopy examinations were performed on all patients at baseline and at the final study visit (Week 6). (Note: A discussion of the trial's endoscopy findings can be found in the HFD-180 medical officer's safety review.) Patients also kept a diary card to record the use of concomitant medications and study related adverse events.

Demographics:

Demographically, all 4 treatment groups were comparable in terms of background characteristics such as race, gender, age, height and weight. The majority of the patients entered were Caucasian (85.8%) and female (66.8%), with a mean age of 62 years . Although the randomization was done via investigator and was not stratified for the joint affected, there were no significant differences noted between the treatment groups in terms of the joint affected or in disease duration. (See Table 1 below.)

Table 1 - Table of OA Disease Characteristics of the Study Population Entered in Study NN2-94-02-349

Characteristic	Diclofenac 75 mg b.i.d (N=154)	Arthrotec I t.i.d. (N=152)	Arthrotec II b.i.d. (N=175)	Placebo (N=91)	P-Value
Joint Affected:					
Hip	25(16%)	34(22%)	26(15%)	10(11%)	0.135
Knee	100(65%)	94(62%)	120(69%)	57(63%)	
Hip and Knee	29(19%)	24(16%)	29(17%)	24(26%)	
Disease Duration (yrs.):					
Mean	11.9	11.9	10.3	10.6	0.389
Range	1 - 50	1 - 57	0 - 40	0 - 34	

There were no significant treatment group differences noted between the treatment groups at the baseline evaluation for the physician's or patient's global assessments ($p \geq 0.092$), OA severity index ($p=0.898$), functional capacity ($p=0.449$), or the patient's assessment of arthritis pain ($p=0.241$).

Disposition:

Fifty-five (55) investigators from the U.S. entered 1 or more patients. A total of 572 patients were randomized into the trial as follows: 154 patients were treated with diclofenac, 152 were treated with Arthrotec I, 175 were treated with Arthrotec II, and 91 were treated with placebo. One hundred three (103) patients discontinued the study due to a variety of reasons as shown in the following table, Table 2. The placebo treatment group had the greatest number of overall premature discontinuations (23%) which were mainly due to lack of efficacy. The numbers of patients that discontinued from the 3 active treatment groups were similar. (See Table 2 below.) The majority of patients who dropped out prematurely from the 3 active treatment groups did so due to adverse events, the incidence of which was not found to be statistically significant (p=0.293) on comparison between the active treatment groups. (Refer to Table 2 below.)

Table 2 - Reasons For Premature Trial Discontinuation From Study NN2-94-02-349

Reason	Diclofenac 75 mg b.i.d (N=154)	Arthrotec I t.i.d. (N=152)	Arthrotec II b.i.d. (N=175)	Placebo (N=91)
Lack of Efficacy:	3(2%)	2(1%)	4(2%)	14(15%)
Adverse Event:	20(13%)	14(9%)	23(13%)	6(6%)
Protocol Deviation:	5(3%)	5(3%)	6(3%)	0(0%)
Lost to Follow-Up:	0(0%)	0(0%)	0(0%)	1(1%)
Total:	28(18%)	21(14%)	33(20%)	21(23%)

p = 0.263

Overall the incidence of adverse events experienced by patients during the trial was similar for all 4 treatment groups: 87.7% (135/154) for the diclofenac treatment group, 85.5% (130/152) for the Arthrotec I treatment group, 89.7% (157/175) for the Arthrotec II treatment group, and 81.3% (74/91) placebo treatment group. The types of adverse events reported by patients (i.e., those not reported on endoscopy) were also similar for the 3 active treatments, and predominantly involved the gastrointestinal tract. (See Table 3 below.)

Table 3 - Incidences of the Most Frequently Reported Drug-Related Adverse Events Not Associated with Endoscopy for Study NN2-95-06-349

Adverse Event	Diclofenac 75 mg b.i.d (N=154) N (%)	Arthrotec I t.i.d. (N=152) N (%)	Arthrotec II b.i.d. (N=175) N (%)	Placebo (N=91) N (%)	Total (N=572) N (%)
Dyspepsia	69(44.8)	52(34.2)	72(41.1)	35(38.5)	228(39.9)
Abdominal Pain	45(29.9)	48(31.6)	51(29.1)	15(16.5)	159(27.8)
Diarrhea	28(18.2)	45(29.6)	38(21.7)	9(9.9)	120(21.0)
Headache	25(16.2)	13(8.6)	18(10.3)	19(20.9)	75(13.1)
Flatulence	19(12.3)	31(20.4)	42(24.0)	8(8.8)	100(17.5)
Constipation	15(9.7)	8(5.3)	11(6.3)	3(3.3)	37(6.5)
Nausea	15(9.7)	20(13.2)	26(14.9)	7(7.7)	68(11.9)
Vomiting	10(6.5)	7(4.6)	5(2.9)	1(1.1)	23(4.0)

(Note: This review is limited to the assessment of drug efficacy. For further discussion of safety and endoscopic evaluations, see the HFD-180 medical officer's safety review.)

No significant differences were noted between the groups in terms of compliance with study medication which was greater than 90% for all 4 treatment groups during all treatment periods.

Efficacy:

The primary endpoint analysis was the Week 6 visit. An intent-to-treat analysis (ITT), with the last observation carried forward as compared to baseline of the 3 primary efficacy variables evaluated is presented in the following table, Table 4. (Note: The Sponsor initially performed categorical analyses of the treatment group comparisons for both the Physician's and Patient's Global assessments and used an observed mean change for the OA Severity Index comparisons, but later redid the primary efficacy analysis using mean changes from baseline with least mean squares (LMS) and calculated the Q-statistic for the 3 primary pairwise comparisons at the request of this reviewing division.)

Table 4- Results of the Week 6 ITT Analysis of the Baseline and Least Squares Mean (LSM) Change of the 3 Primary Efficacy Variables Evaluated In Study NN2-95-06-349

Efficacy Variable	Diclofenac 75 mg b.i.d (N=154)	Arthrotec I t.i.d. (N=152)	Arthrotec II b.i.d. (N=175)	Placebo (N=91)
Physician's Global:				
Categorical-*				
Improved	45.4%	46.1%	53.1%	31.9%
Unchanged	53.9%	53.9%	46.3%	68.1%
Worsened	0.6%	0.0%	0.6%	0.0%
Baseline Mean	3.86	3.84	3.59	3.85
LSM Change**	-1.03	-1.10	-1.16	-0.64
Patient's Global:				
Categorical-*				
Improved	51.3%	45.4%	54.3%	31.9%
Unchanged	48.1%	54.6%	45.7%	64.8%
Worsened	0.6%	0.0%	0.0%	3.3%
Baseline Mean	3.99	3.87	3.94	3.84
LSM Change**	-1.12	-1.14	-1.23	-0.63
OA Severity Index:				
Baseline Mean	14.2	14.0	14.0	13.9
LSM Change**	-3.55	-3.18	-3.72	-0.92

* Note: "Improved" or "worsened" from baseline was pre-defined by the Sponsor as a decrease or increase, respectively, of 2 or more units.
** Note: A negative value denotes improvement from baseline.

The p-values for the principal pairwise comparisons and their respective Q-ratios and qL values to determine the comparability of the test drug(s) with the active control for the Week 6 time point are shown in Table 5 (see below). [Note: The Q statistic is the ratio of the least squares mean change from baseline between test drug (Arthrotec) and active control (diclofenac). The qL value is the lower end of its associated 95% 2-sided confidence interval. For OA trials an acceptable Q ratio and qL value are $0.80 \leq Q \leq 1.20$ and 0.60 respectively.]

This trial demonstrated that there were no statistically significant differences between the diclofenac treated group and either the Arthrotec I or II treatment groups for all 3 primary efficacy variables at the primary endpoint, Week 6 (Arthrotec I vs diclofenac: Physician's Global - categorical: p=0.609, LSM: p=0.508; Patient's Global - categorical: p=0.336, LSM: p=0.909; OA Severity Index - LSM: p=0.400; Arthrotec II vs diclofenac: Physician's Global - categorical: p=0.380, LSM: p=0.198; Patient's Global - categorical: p=0.504, LSM: p=0.364; OA Severity Index - LSM: p=0.701). (See Table 5

below.) The comparability of Arthrotec I vs diclofenac, and Arthrotec II vs diclofenac, is further supported by the capturing of 3 out of the 3 Q ratios and q[L] values for the primary efficacy variables by both treatments (Arthrotec I vs diclofenac - Physician's Global: 1.07[0.88], Patient's Global: 1.01[0.83], OA Severity Index: 0.90[0.69]; Arthrotec II vs diclofenac - Physician's Global: 1.13[0.93], Patient's Global: 1.09[0.90], OA Severity Index: 1.05[0.82]). (Refer to Table 5 below.)

Table 5 - Table of P-Values, Q-Ratios and qL values from the Week 6 ITT Analysis of the Primary Pairwise Comparisons of Study NN2-95-06-349

Efficacy Variable	Diclofenac 75 mg b.i.d. vs. Placebo	Arthrotec I t.i.d. vs. Diclofenac	Arthrotec II b.i.d. vs. Diclofenac
Physician's Global:			
Categorical	p=0.076	p=0.609	p=0.389
LSM	p=0.002*	p=0.508	p=0.198
Q [qL]		1.07[0.88]	1.13[0.93]
Patient's Global:			
Categorical	p=0.006**	p=0.336	p=0.504
LSM	p<0.001*	p=0.909	p=0.364
Q [qL]		1.01[0.83]	1.09[0.90]
OA Severity Index:			
LSM	p<0.001*	p=0.400	p=0.701
Q[qL]		0.90[0.69]	1.05[0.82]

* Statistically significant p-values
** Note: Statistically significant at the 5% level for primary pairwise comparisons using Hochberg's step-down procedure. The largest of the p-values for the 3 primary pairwise comparisons is considered statistically significant if it is ≤ 0.05, the next smaller if it is ≤ 0.025, and the smallest if it is ≤ 0.0167.

Although diclofenac 75 mg BID was not shown to be a statistically more effective treatment than placebo on categorical analysis of the Physician's Global (p=0.076), a statistically significant difference was shown on the LSM Change analysis of this efficacy variable (p=0.002). Diclofenac 75 mg BID was also shown to be significantly more effective than placebo for both the Patient's Global (categorical: p=0.006, LSM Change: p<0.001) and the OA Severity Index (LSM Change: p<0.001). (See Table 5 above).

Secondary pairwise comparisons of the categorical analysis for the 2 primary global efficacy variables and the observed change from baseline for the third primary efficacy variable, the OA Severity Index, showed that while both Arthrotec I and II were significantly more effective than placebo at Week 6 ($p \leq 0.029$), they were not significantly different when compared against each other ($p \geq 0.199$). (Refer to Table 6 below.)

Table 6 - Table of P-Values of the Secondary Pairwise Comparisons from the Week 6 ITT Analysis of Study NN2-95-06-349

Efficacy Variable	Arthrotec I t.i.d. vs. Placebo	Arthrotec II b.i.d. vs. Placebo	Arthrotec I t.i.d. vs. Arthrotec II b.i.d.
Physician's Global:			
Categorical	p=0.029*	p=0.003*	p=0.266
Patient's Global:			
Categorical	p=0.013*	p<0.001*	p=0.109
OA Severity Index:			
LSM	p<0.001*	p<0.001*	p=0.256

* Statistically significant p-values

The above findings are further supported by the results of the ITT Week 2 analysis (not shown) which were very similar to those of the Week 6 analysis, and the analysis of the secondary variables (a patient's assessment of arthritis pain via a 10 cm VAS, a functional capacity classification, and incidence of patient withdrawal due to lack of OA efficacy). The results from the analysis of the secondary variables are shown in the following table, Table 7. Although diclofenac 75 mg BID was not shown to be a statistically more effective treatment than placebo by Hochberg's step-down procedure (p= 0.023) for the variable of Functional Capacity Classification, statistically significant differences were shown on secondary pairwise comparisons for Arthrotec I and II versus placebo ($p \leq 0.031$) for this assessment. (See Table 7 below.)

Table 7 - Table of P-Values from the ITT Analysis of the Secondary Efficacy Parameters at Week 6 of Study NN2-95-06-349

	Primary Pairwise Comparisons			Secondary Pairwise Comparisons		
Efficacy Variable	Diclof. vs. Placebo	Arthro. I vs. Diclof.	Arthro. II vs. Diclof.	Arthro. I vs. Placebo	Arthro. II vs. Placebo	Arthro. I vs. Arthro II
Patient's Assessment Of Pain (VAS):	*	p=0.350	p=0.339	p=0.002**	p<0.001**	p=0.056
Functional Capacity Classification:	p=0.023	p=0.998	p=0.234	p=0.024**	p=0.031**	p=0.213
Withdrawal Due to Lack Efficacy:	*	p=0.663	p=0.832	p<0.001**	p<0.001**	p=0.515

* Note: Statistically significant at the 5% level for primary pairwise comparisons using Hochberg's step-down procedure. The largest of the p-values for the 3 primary pairwise comparisons is considered statistically significant if it is ≤ 0.05, the next smaller if it is ≤ 0.025, and the smallest if it is ≤ 0.0167.

** Statistically significant p-values.

A quality of life analysis (i.e., the SF-36) was added as another secondary efficacy variable after the trial was already underway. A total of 187 patients were able to participate and complete the SF-36. In summary, no statistically significant difference was shown at the baseline SF-36 evaluation on comparison of the 4 treatment groups ($p \geq 0.374$). There were statistically significant mean improvements over baseline scores in physical functioning, bodily pain, and social functioning ($p \leq 0.047$) for the diclofenac, Arthrotec I and II treatment groups as compared to the placebo group at Week 2. The improvement over baseline score for those 3 components and to the role-physical component of the SF-36 was also noted at the Week 6 visit ($p \leq 0.016$).

Reviewer's Comments

When the Sponsor designed this trial they chose to study 3 primary efficacy variables one of which, the OA Severity Index, is a composite assessment that has not been commonly used in previous commercial NSAID trials reviewed by this division. The OA Severity Index is a comprehensive assessment of joint pain as related to both activity and inactivity. It is composed of several different assessments which measure pain on walking, sitting, standing, during activities of daily living, at night, and morning stiffness. It is therefore redundant to use the OA Severity Index as a primary efficacy parameter in a clinical trial if a categorical Patient's Global assessment is also used. Instead, a Patient's Pain Assessment measured via a 10 cm VAS is commonly employed as a primary efficacy parameter.

In this trial there was some duplication of effort since the Sponsor used both the OA Severity Index and Patient's Global assessments as primary efficacy variables. The Sponsor did use the traditional Patient's Pain Assessment (via 10 cm VAS) as a secondary efficacy variable in this study, which showed that treatment with diclofenac, Arthrotec I and II were all significantly better than placebo. Although the diclofenac treated group failed to beat placebo in terms of the categorical analysis for the Physician's Global Assessment, it did do so on the least square mean analysis for this variable, while at the same time it captured the other 2 primary efficacy variables. Diclofenac's efficacy as an NSAID in the treatment OA was also supported by its capturing the same secondary efficacy variables as Arthrotec I and II, to which it was not found to be statistically different. In addition, both Arthrotec I and II were shown to be significantly better than placebo on the secondary pairwise comparisons by capturing 3 out of the 3 primary efficacy variables. Thus there is no question in this medical reviewer's mind that the formulation of diclofenac used in this trial was a valid active comparator, which is important since the validity of the active comparator directly affects the results of the Q statistics used to establish comparability between active treatments. Besides being affected by the validity of the active comparator, the Q statistics are also influenced by the sample size. This trial was designed to study a relatively large sample of patients (n=150) in each of the active treatment groups. It

should be noted that here was a slight discrepancy in the sample size of the Arthrotec II arm of the trial in which 175 patients were enrolled. Neither I nor the reviewing statistician could find justification on the part of the Sponsor for doing this. Despite this "padding" of the Q statistic, the active treatments were numerically similar in terms of overall responses to therapy, and dropout due to lack of efficacy.

In summary, this trial demonstrates that while both Arthrotec I and II are comparable in terms of efficacy to 75 mg BID of the diclofenac formulation used in this trial, they are significantly more efficacious than placebo in the treatment of osteoarthritis.

A COMPARISON OF DICLOFENAC/MISOPROSTOL AND DICLOFENAC/PLACEBO IN THE TREATMENT OF OSTEOARTHRITIS.

Protocol IN2-89-02-298

Design:

This was a multi-center, double-blind, randomized trial with 2 parallel treatment arms in which patients with American College of Rheumatology (ACR) functional class I-III OA of the knee and/or hip were randomized to receive either fixed combination tablets containing diclofenac 50 mg/misoprostol 200 mcg (Arthrotec I) or fixed combination tablets containing diclofenac 50 mg/placebo b.i.d. or t.i.d. for 4 weeks. Patients' assignments to either the b.i.d. or t.i.d. dosage regimens was at the discretion of the treating investigator and was based on each individual patients' needs. The dosages of the study medications could be changed during the trial at the Week 2 visit, depending on patients' responses to the arthritis therapy. Patients were not required to demonstrate a baseline flare of their arthritis in order to be entered into this trial. Efficacy and safety evaluations were performed at the baseline visit, and at Weeks 2 and 4 of the study. All patients were evaluated for the following three primary efficacy parameters for OA: the physician's global assessment and the patient's global assessment of arthritis condition via categorical scales; and the OA severity index. The OA severity index was a composite score, based on a maximum score of 24, comprised of various patient self-assessments related to the following: severity of OA pain, walking distance and activities of daily living. Secondary efficacy variables were also performed and included: the patient's assessment of arthritis joint pain via a visual analogue scale (VAS), a functional capacity classification, and an articular index of joint tenderness. The articular index of joint tenderness was another composite score based on patient responses to joint margin pressure or passive joint movement for 48 joints or joint groups. Safety was assessed by routine lab analyses, physical exams and adverse event monitoring. Patients also kept a diary card to record the use of concomitant medications and study related adverse events.

Demographics:

Demographically, both treatment groups were comparable in terms of background characteristics. The majority of the patients entered were Caucasian (97%) and female (63%), with a mean age of 62.3 years . The average duration of disease (OA) was 5.8 years and was similar for both groups. There were no significant differences (p=0.594) noted between the groups in dosage regimen assigned at trial entry. (Refer to Table 8 below.) The distribution of the target joint studied was similar for both groups. (See Table 8.)

Table 8 - Table of OA Disease Characteristics of the Study Population Entered in Study IN2-89-02-298

Characteristic	Diclofenac 50 mg/ Placebo (N=227)	Diclofenac 50 mg/ Misoprostol 200 mcg (N=228)
Joint Affected:		
Hip	44(19%)	54(24%)
Knee	144(63%)	143(63%)
Hip and Knee	39(17%)	31(14%)
Dosage Regimen Assigned:		
BID	151(67%)	157(69%)
TID	76(34%)	71(31%)

There were no significant differences noted between the treatment groups at the baseline evaluation for the Physician's Global (p=0.922), Patient's Global (p=0.131), OA Severity Index (p=0.530), Functional Capacity (p=0.242), or the Patient's Assessment of Joint Pain (p=0.570).

Disposition:

Forty-three (43) of the participating investigators entered 1 or more patients. Four hundred fifty-five (455) patients were randomized into the trial as follows: 228 patients were treated with diclofenac/misoprostol and 227 were treated with diclofenac/placebo. Seventy-eight (78) patients discontinued the study due to a variety of reasons as shown in Table 9. (See below.) The diclofenac/misoprostol treatment group had the greatest number of overall premature discontinuations (50/228, 21.9%) which were mainly due to adverse events. (For further discussion of trial safety see HFD-180 medical officer's safety review.)

Table 9 - Reasons For Premature Trial Discontinuation From Study IN2-89-02-298

Reason	Diclofenac 50 mg/ Placebo b.i.d.- t.i.d. (N=227)	Diclofenac 50 mg/ Misoprostol 200 mcg b.i.d.-t.i.d. (N=228)	Total
Lack of Efficacy:	2(0.9%)	5(2.2%)	7
Adverse Event:	24(10.6%)	38(16.7%)	62
Protocol Deviation:	2(0.9%)	5(2.2%)	7
Lost to Follow-Up:	0(0)	2(0.9%)	2
Total:	28(12.3%)	50(21.9%)	78

Although 84% of the patients from each treatment group remained on the dosage regimen to which they were assigned on admission to the trial, there was a statistically significant difference noted between treatment groups for patient compliance of study medication ingested b.i.d. during the time interval between the baseline and Week 2 visit (p=0.020) in favor of the diclofenac/placebo group (diclofenac/placebo: mean compliance of 105.7%, diclofenac/misoprostol group: mean compliance of 96.6%, (Note: The Sponsor did not consider this difference to be clinically meaningful since the calculations included only patients who returned their study medication containers to the participating study sites.) No significant differences were noted between the treatment groups for the other time intervals or for the t.i.d. dose regimen.

Efficacy:

The primary endpoint analysis was the Week 4 visit. An intent-to-treat analysis (ITT), or last observation carried forward as compared to baseline, of the 3 primary efficacy variables evaluated is presented in the following table, Table 10 (see below).

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Table 10- Results of the Week 4 ITT Analysis of the Change from Baseline and the Least Squares Mean (LSM) of the 3 Primary Efficacy Variables Evaluated In Study IN2-89-02-298

Efficacy Variable	Diclofenac/ Placebo b.i.d.-t.i.d. (N=227)	Diclofenac/ Misoprostol b.i.d.-t.i.d. (N=228)	P-Value	Q ratio* and q[C. I.]
Physician's Global:				
Categorical-**				
Improved	24%	15%		
Unchanged	67%	68%		
Worsened	0%	0%	p=0.015	
Unknown	9%	16%		
Baseline Mean	3.23	3.19		0.99[0.96,1.07]
LSM	2.30	2.50		1.09[1.02,1.16]
Patient's Global:				
Categorical-**				
Improved	22%	23%		
Unchanged	67%	60%		
Worsened	1%	1%	p=0.151	
Unknown	9%	16%		
Baseline Mean	3.25	3.33		1.03[0.99,1.07]
LSM	2.42	2.56		1.01[0.96,1.06]
OA Severity Index:				
Mean Change***	-3.39	-2.90	p=0.281	
Baseline Mean	12.02	11.78		0.98[0.93,1.03]
LSM	8.71	9.19		1.06[0.93,1.05]

* Note: The Q value is the ratio of the actual mean (baseline) or least squares mean (week 4) between Diclofenac/Misoprostol and Diclofenac/Placebo rather than the least squares mean improvement from baseline. The rationale for using the actual mean score rather than the mean improvement by the Sponsor was that the room for improvement would be too small for a stable denominator in Q since the patients were not flared at baseline. The numbers in the bracket are the lower and upper 95% confidence intervals of Q.

** Note: "Improved" or "worsened" from baseline was pre-defined by the Sponsor as a decrease or increase, respectively, of 2 or more units.

*** Note: A negative value denotes improvement from baseline.

This trial demonstrated that there were no statistically significant differences between the 2 treatment groups for 2 out of the 3 primary efficacy variables (Patient's Global: p=0.151; OA Severity Index: p=0.281). The Diclofenac/Placebo treatment group did significantly better than the Diclofenac/Misoprostol treatment group in terms of the Physician's Global Assessment (p=0.015). (See Table 10 shown above.) On a

modified ITT analysis where the unknown group was eliminated, the Physician's Global Assessment was no longer found to be statistically significant (p=0.65). In terms of comparability, the Diclofenac/Misoprostol treatment group captured 3 out of the 3 Q ratios and q[L] values for the primary efficacy variables. (Refer to Table 10 shown above for the actual numerical values.) (Note: In calculating the Q values for this trial, the Sponsor used the actual mean at baseline or the least squares mean at Week 4 between the two treatments rather than the least squares mean improvement from baseline since they felt that there would not be enough room for improvement in this non-flare trial for a stable denominator in Q.) The Sponsor also did a subset analysis of patients based on the target joint studied (i.e., knee or hip). The results of this target joint analysis were similar to the results of the combined Week 4 ITT analysis shown in the preceding table, Table 10. The results of the Week 4 evaluable cohort analysis (not shown) were similar to the results of the Week 4 ITT shown in Table 10 (see above) except that no significant difference between treatments was shown to exist for the Physician's Global Assessment (p=0.306).

The intent-to-treat (ITT) analysis of the secondary efficacy parameters demonstrated that there were no statistically significant differences between the 2 treatment groups for 2 out of the 3 primary efficacy variables (Articular Index of Joint Tenderness: p=0.584; Change in Functional Capacity: p=0.559). A significant difference in improvement in the Patient's Assessment of Joint Pain for the Diclofenac/Misoprostol treatment group (p=0.034) was noted by the Sponsor who stated that while this finding was statistically significant, its true significance was questionable due to the unequal number of responses to the 6 parameters that comprised this variable.

Reviewer's Comments

This medical reviewer found the results of this trial difficult to interpret because it was a "non-flared" study and the individual dosing regimens were permitted to change during the trial as needed for efficacy. The presence of a placebo-controlled group would have been helpful in light of these design flaws as well as putting the higher number of dropouts from the diclofenac/misoprostol treatment group due to lack of efficacy and drug-related adverse events into perspective. The modified Q analysis is also problematic since the reviewing division has virtually no experience with this type of modified analysis (see biostatistician's review), since it presents a way to get around the fact that this was a non-flared trial. When one looks at the categorical responses to the Physician's and Patient's Global Assessments for both treatments, they numerically "trend" together but any statistically significant difference is lost when the "unknown" group is dropped from the calculations (i.e., the modified ITT and evaluable cohort analysis). At best, one may conclude that while both treatments are comparable, treatment with diclofenac/placebo may in fact be slightly more efficacious then with diclofenac/misoprostol.

A COMPARISON OF THE EFFICACY AND UPPER GASTROINTESTINAL SAFETY OF DICLOFENAC/MISOPROSTOL AND DICLOFENAC/PLACEBO IN THE TREATMENT OF PATIENTS WITH OSTEOARTHRITIS (OA).

Protocol IN2-89-02-296

Design:

This was a multi-center, double-blind trial with 2 parallel treatment arms in which patients with American College of Rheumatology (ACR) functional class I-III OA of the knee and/or hip were randomized to receive either fixed combination tablets containing diclofenac 50 mg/misoprostol 200 mcg (Arthrotec I) or fixed combination tablets containing diclofenac 50 mg/placebo b.i.d. or t.i.d. for 4 weeks. Patients' assignments to either the b.i.d. or t.i.d. dosage regimens was at the discretion of the treating investigator and was based on each individual patients' needs. The dosages of the study medications could be changed during the trial at the Week 2 visit, depending on patients' responses to the arthritis therapy. Patients were not required to demonstrate a baseline flare of their arthritis in order to be entered into this trial.

Efficacy and safety evaluations were performed at the baseline visit, and at Weeks 2 and 4 of the study. All patients were evaluated for the following three primary efficacy parameters for OA: the Physician's Global Assessment and the Patient's Global Assessment of arthritis condition via categorical scales; and the OA Severity Index. The OA severity index was a composite score, based on a maximum score of 24, comprised of various patient self-assessments related to the following: severity of OA pain, walking distance and activities of daily living. Secondary efficacy variables were also performed and included: the Patient's Assessment of Arthritis Joint Pain via a visual analogue scale (VAS), a Functional Capacity Classification, and an Articular Index of Joint Tenderness. The articular index of joint tenderness was another composite score based on patient responses to joint margin press or passive joint movement for 48 joints or joint groups. Safety was assessed by upper endoscopy, routine lab analyses, physical exams and adverse event monitoring. Upper GI endoscopy examinations were performed on all patient's at baseline and at the final study visit (Week 4). (Note: A discussion of the trial's endoscopy findings can be found in the HFD-180 medical officer's safety review.) Patients also kept a diary card to record the use of concomitant medications and study related adverse events.

Demographics:

Demographically, the only background characteristic that was found to be statistically significantly different between the 2 treatment groups was weight (mean weight of 70.4 kg for the diclofenac/misoprostol group versus mean weight of 73.8 kg

for the diclofenac/placebo group, p=0.004). The majority of the patients who participated in the trial were Caucasian (88%) and female (73%), with a mean age of 60.3 years . The average duration of disease (OA) was 7.35 years, and was similar for both groups. The 2 groups were also similar in terms of the distribution of the target joint studied. (See Table 11 below.)

Table 11 - Table of OA Disease Characteristics of the Study Population Entered in Study IN2-89-02-296

Characteristic	Diclofenac 50 mg/ Placebo b.i.d.-t.i.d. (N=183)	Diclofenac 50 mg/ Misoprostol 200 mcg b.i.d.-t.i.d. (N=178)
Joint Affected:		
Hip	25(14%)	27(15%)
Knee	111(61%)	144(54%)
Hip and Knee	47(26%)	39(30%)

There were no significant treatment group differences noted between the treatment groups at the baseline evaluation for the Physician's Global Assessment (p=0.981), Patient's Global Assessments (p=0.802), OA Severity Index (p=0.783), Functional Capacity (p=0.583), Articular Index of Joint Tenderness (p=0.406) or the Patient's Assessment of Joint Pain (p=0.622).

Disposition:

Thirty-two (32) of the participating international investigators entered 1 or more patients. Three hundred sixty-one (361) patients were randomized into the trial as follows: 178 patients were treated with diclofenac/misoprostol and 183 were treated with diclofenac/placebo. Approximately 87% of the diclofenac/misoprostol patients and 89% of the diclofenac/placebo patients continued to take the dosage regimen assigned at trial entry. No significant differences were noted between the groups in terms of the numbers of patients who changed their study medication dosage regimen during the trial (p=0.454).

Thirty-eight (38) patients discontinued the study due to a variety of reasons as shown in Table 12. (See below.) The numbers of patients who dropped-out of the trial were similar for both treatment groups. No patients prematurely discontinued the trial due to lack of efficacy.

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Table 12 - Reasons For Premature Trial Discontinuation From Study IN2-89-02-296

Reason	Diclofenac 50 mg/ Placebo BID-TID (N=183)	Diclofenac 50 mg/ Misoprostol 200 mcg BID-TID (N=178)	Total
Lack of Efficacy:	0(0%)	0(0%)	0
Adverse Event:	11(6.0%)	10(5.6%)	21
Protocol Deviation:	3(1.6%)	3(1.7%)	6
Lost to Follow-Up:	6(3.3%)	5(2.8%)	11
Total:	20(10.9%)	18(10.1%)	38

For both treatment groups compliance with medications was greater than 90% and no significant differences ($p \geq 0.291$) were noted between the treatment groups over time, nor for either dosage regimen (BID vs TID).

Efficacy:

The primary endpoint analysis was the Week 4 visit. An intent-to-treat analysis (ITT), or last observation carried forward as compared to baseline, of the 3 primary efficacy variables evaluated is presented in the following table, Table 13 (see below).

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Table 13- Results of the Week 4 ITT Analysis Change From Baseline and Least Squares Mean (LSM) of the 3 Primary Efficacy Variables Evaluated In Study IN2-89-02-296

Efficacy Variable	Diclofenac 50 mg/ Placebo b.i.d.-t.i.d. (N=183)	Diclofenac 50 mg/ Misoprostol 200 mcg b.i.d.-t.i.d. (N=178)	P-Value	Q ratio* and q[C.I.]
Physician's Global:				
Categorical-"				
Improved	14%	12%		
Unchanged	78%	78%		
Worsened	1%	2%	p=0.681	
Unknown	10%	7%		
Baseline Mean	3.00	3.00		1.00[0.96,1.04]
LSM	2.36	2.33		0.99[0.93,1.05]
Patient's Global:				
Categorical-"				
Improved	18%	21%		
Unchanged	74%	69%		
Worsened	1%	0%	p=0.290	
Unknown	7%	10%		
Baseline Mean	3.12	3.21		1.03[0.99,1.07]
LSM	2.40	2.30		0.96[0.90,1.03]
OA Severity Index:				
Mean Change""	-2.99	-2.50	p=0.469	
Baseline Mean	11.51	11.39		0.99[0.93,1.05]
LSM	8.85	8.89		1.01[0.93,1.09]

* Note: The Q value is the ratio of the actual mean (baseline) or least squares mean (week 4) between Diclofenac/Misoprostol and Diclofenac/Placebo rather than the least squares mean improvement from baseline. The rationale for using the actual mean score rather than the mean improvement by the Sponsor was that the room for improvement would be too small for a stable denominator in Q since the patients were not flared at baseline. The numbers in the bracket are the lower and upper 95% confidence intervals of Q.

" Note: "Improved" or "worsened" from baseline was pre-defined by the Sponsor as a decrease or increase, respectively, of 2 or more units.

"" Note: A negative value denotes improvement from baseline.

This trial demonstrated that there were no statistically significant differences between the 2 treatment groups for 3 out of the 3 primary efficacy variables (Physician's Global: p=0.681; Patient's Global: p=0.290; OA Severity Index: p=0.469). In terms of comparability, the diclofenac/misoprostol treatment group captured 3 out of the 3 Q ratios and q[L] values for the primary efficacy variables. (Refer to Table 13 shown above for the actual numerical values.) (Note: In calculating the Q values for this trial, the Sponsor used the actual mean at baseline or the least squares mean at Week 4